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EP04/7980

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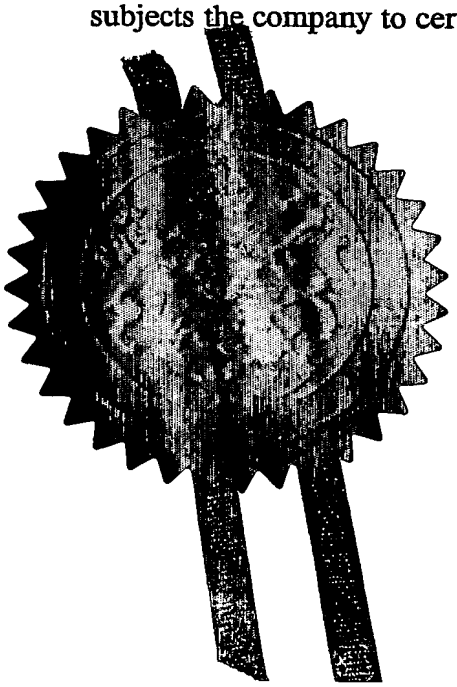

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Dated 20 MAY 2004

Patents Form 1/77

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1/77

16JUL03 E822818-1 D00245
P01/7700 0.00-0316546.1

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
South Wales NP10 8QQ

1.	Your reference	4-33277P1
2.	Patent application number *(The Patent Office will fill in this part)*	0316546.1
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
		7125487005
4.	Title of invention	Process for the Manufacture of Organic compounds
5.	Name of your agent *(If you have one)*	Bernard Marsh
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham, West Sussex RH12 5AB
	Patents ADP number *(if you know it)*	07181522002 ✓

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*	Yes
	a) any applicant named in part 3 is not an inventor, or	
	b) there is an inventor who is not named as an applicant, or	
	c) any named applicant is a corporate body.	
	(see note (d))	

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	32
Claim(s)	6
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	One
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature — Date

15th July 2003

12. Name and daytime telephone number of person to contact in the United Kingdom — Mrs. S. Schnerr — 01403 323069

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Notes

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Process for the Manufacture of Organic Compounds

The invention relates to a method for preparing substituted tetrazoles, compounds obtained according to this method, new reactants and new tetrazole derivatives.

Tetrazoles are structural elements, for example, of pharmaceuticals or agricultural compositions, foaming agents, automotive inflators, and the like. Especially mentioned are the class of so-called angiotensin II receptor antagonists also designated nowadays as angiotension receptor blockers (ARBs) that can be used e.g. for the treatment of hypertension and congestive heart failure. Most of said ARBs comprise a 5-tetrazole element in the structure.

It is known in the art that tetrazole derivatives can be prepared by reacting various nitriles with organic azides in relative good yields. Representatives of corresponding azides are, for example, organo-tin azides which have some toxic profile. They have to be handled with special care in production processes, cause ecological problems and require a significant amount of additional process work to recycle them from the wastewater thereby additionally increasing the production costs. Tetrazole forming methods which use trialkylammonium azides or tetraalkylammonium azides may form volatile sublimates in the reaction reactors at higher temperatures which have the risk of explosion and are therefore not easy to handle in large scale production.

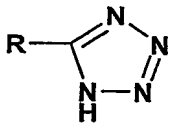
There is a strong need to develop process variants, new reagents and intermediates that avoid the above-mentioned disadvantages. Especially, a lot of effort has been made to substitute corresponding organo-tin azides with alternative agents which are viable alternatives in the production of tetrazoles with sufficiently high yields.

It has surprisingly been found that organo boron azides and aluminium azides can be used as alternatives to corresponding organo-tin compounds. Said boron and aluminium compounds are, available in considerably large scales, and relatively inexpensive, especially corresponding aluminium compounds that are produced for the polymer industry (e.g. Ziegler-Natta catalysis). It has surprisingly turned out that high yields of tetrazoles can be achieved when using these organo azides to be used according to the present invention. Furthermore, as the corresponding boron and aluminium azides are not known to be toxic,

their use does not require special care when recycling the waste water and moreover the dialkylmetal azides can be produced in a large scale at low costs and mild conditions. Even though, corresponding dialkyl boron and dialkyl aluminium azides have these advantages, they have not been described in the literature to be used in [2+3]cycloadditions with nitriles to form tetrazoles. What is known from the literature is that e.g. di-organyl aluminium azides can be used to open epoxides and also to form acyl-azides from esters. However, the use of di-organyl boron or di-organyl aluminium azides, respectively, to form tetrazoles with nitriles is fully surprising.

The present invention relates to the use of oragno boron and organo aluminium azides, especially as defined below, for the manufacture of tetrazole derivatives.

The present invention relates to a process for the manufacture of a tetrazole of formula



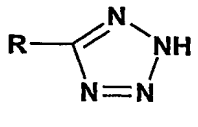
(I)

or a tautomer or a salt thereof, wherein R represents an organic residue;
comprising

(i) reacting a compound of formula **R-CN (II a)** with an azide of formula **$(R_1)(R_2)M\text{-}N_3$ (II b)**, wherein R has the meaning as defined above; R_1 and R_2, independently of another, represent an organic residue such as an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or an heteroaraliphatic residue, each residue, independently of another, being unsubstituted or substituted; and M is boron or aluminium; and

(ii) isolating the resulting compound of formula (I).

A tautomer of a compound of formula (I) is a compound of formula



(I').

A salt of a compound of formulae (I) or (I')

The general definitions used above and below of the corresponding residues, unless otherwise defined below, have the following meanings:

An organic residue is, for example; an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or an heteroaraliphatic residue, each residue, independently of one another, being unsubstituted or substituted.

An aliphatic residue is, for example, alkyl, alkenyl or secondarily alkynyl, each of which can be interrupted by NH, substituted NH, O, or S; and each of which can be unsubstituted or substituted, for example, mono-, di- or tri-substituted.

Alkyl is, for example, C_1-C_{20}-alkyl, in particular C_1-C_{10}-alkyl. C_1-C_8-alkyl is preferred.
Alkenyl is, for example, C_3-C_{20}-alkenyl, in particular C_3-C_{10}-alkenyl. Preferred is C_3-C_5-alkenyl; for example, 2-propenyl or 2- or 3-butenyl.
Alkinyl is, for example, C_3-C_{20}alkynyl, in particular C_3-C_{10}alkynyl. Preferred is C_3-C_5alkynyl such as propargyl.

Alkyl, alkenyl or alkynyl that can be interrupted by NH, O or S is in particular C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, -C_3-C_{20}-alkenyl or - C_3-C_{20}-alkynyl, or C_3-C_{20}-alkenyloxy- C_1-C_{20}-alkyl, - C_3-C_{20}-alkenyl or - C_3-C_{20}-alkynyl, for example, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, -C_3-C_{10}-alkenyl or - C_3-C_{10}-alkynyl, or C_3-C_{10}-alkenyloxy-C_1-C_{10}-alkyl, -C_3-C_{10}-alkenyl or - C_3-C_{10}-alkynyl. Preferred is C_1-C_7-alkoxy-C_1-C_7-alkyl, -C_3-C_7-alkenyl or - C_3-C_7-alkynyl, or C_3-C_7-alkenyloxy-C_1-C_7-alkyl, -C_3-C_7-alkenyl or - C_3-C_7-alkynyl.

An alicyclic residue is, for example, cycloalkyl and secondarily cycloalkenyl, each of which can also be substituted.
Cycloalkyl in particular C_3-C_8cycloalkyl. Preferred is cyclopentyl and cyclohexyl.
Cycloalkenyl is in particular C_3-C_7cycloalkenyl and is preferably cyclopent-2- and -3-enyl, or cyclohex-2- and -3-en-yl.

A heteroalicyclic residue is, for example, an alicyclic residue, wherein at least one carbon atom is replaced by a heteroatom, e.g. NH, substituted NH, O, or S, each of which can also be substituted.

A carbocyclic aromatic residue is, for example, a mono- or polycyclic or benzoanellated carbocyclic residue, such as phenyl, naphthyl, but also biphenyl, each of which can also be substituted.

A heterocyclic aromatic residue is, for example, 5- or 6-membered and monocyclic radical which has up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom, each of which can also be substituted. Appropriate 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered radicals are in particular pyridyl.

Alkyl, alkenyl, or alkinyl can also be substituted, for example, by a substituent selected from the group consisting e.g. of an alicyclic residue, a heteroalicyclic residue; a carbocyclic and a heterocyclic aromatic residue; each residue, independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents, for example, selected from the group consisting of halogen, amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

Alicyclic or heteroalicyclic residues can also be substituted, for example, by one or more, e.g. two or three, substituents selected from the group consisting e.g. of an aliphatic residue, alicyclic residue, a heteroalicyclic residue; a carbocyclic and a heterocyclic aromatic residue; each residue, independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents, for example, selected from the group consisting of halogen; amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

An alicyclic-aliphatic residue, a heteroalicyclic-aliphatic residue, an araliphatic residue or a heteroaraliphatic residue, each residue (e.g. in both the alicyclic and the aliphatic moiety), independently of another, being unsubstituted or substituted by one or more, e.g. two or

three, substituents in both structural elements, for example, selected from the group consisting of an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic aromatic residue, a heterocyclic aromatic residue; an araliphatic residue; an heteroaraliphatic residue, halogen; amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

A carbocyclic or a heterocyclic aromatic residue can also be substituted, for example, by one or more, e.g. two or three, substituents selected from the group consisting e.g. of an aliphatic residue, alicyclic residue, a heteroalicyclic residue; a carbocyclic and a heterocyclic aromatic residue; each residue, independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents, for example, selected from the group consisting of halogen; amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy.

Halogen is in particular halogen of atomic number not more than 53.

Substituted mercapto is, for example, substituted by an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or an heteroaraliphatic residue, each residue, independently of another, being unsubstituted or substituted by one or more, e.g. two or three, substituents, for example, selected from the group consisting of halogen; amino, substituted amino, mercapto, substituted mercapto, hydroxyl, etherified hydroxyl, carboxy, and amidated carboxy..

Etherified hydroxyl is, for example, hydroxyl etherified by an aliphatic, an alicyclic, heteroalicyclic, an araliphatic, a heteroaryl-aliphatic, a carbocyclic aromatic or heteroaromatic alcohol, each of which can also be substituted.

Esterified carboxyl is, for example, carboxyl which is esterified by an alcohol which is derived from an aliphatic or araliphatic hydrocarbon radical, such as alkyl, phenyl-alkyl, alkenyl and secondarily alkynyl, and which may be interrupted by -O-, such as alkoxy-alkyl, -alkenyl and - alkynyl. Examples which may be mentioned

are C_1-C_7alkoxy-, phenyl-C_1-C_7alkoxy-, C_2-C_7alkenyloxy- and C_1-C_7alkoxy-C_1-C_7alkoxy-carbonyl.

Amidated carboxyl is, for example, carbamoyl in which the amino group is unsubstituted or monosubstituted or, independently of one another, disubstituted by an aliphatic or araliphatic hydrocarbon radical or disubstituted by a divalent aliphatic hydrocarbon radical which may be interrupted by O or may be condensed at two adjacent carbon atoms with a benzene ring, in particular alkylene or lower alkyleneoxy-alkylene. Examples of appropriately substituted amino groups which may be mentioned are C_1-C_7alkyl-, C_2-C_7alkenyl-, C_2-C_7alkynyl-, phenyl-C_1-C_7alkyl-, phenyl-C_2-C_7alkenyl-, phenyl-C_2-C_7alkynyl-, di-C_1-C_7alkyl-, N- C_1-C_7alkyl-N-phenyl-C_1-C_7alkyl- and diphenyl-C_1-C_7alkylamino and also quinol-1-yl, isoquinol-2-yl, C_1-C_7alkylene- and C_1-C_7alkyleneoxy-C_1-C_7alkylene-amino.
Alkylene is, for example, C_1-C_{10}alkylene, in particular, C_1-C_7alkylene, for example methylene, ethylene, or 1,5-pentylene.

Substituted amino has the meanings indicated in connection with substituted carbamoyl and is furthermore acylamino, such as lower alkanoyl-, phenyl-alkanoyl-, benzoyl-, alkanesulfonyl- or benzenesulfonylamino.

Acetalised formyl is, for example, di-alkoxymethyl or oxy-alkyleneoxymethylene.

Alkanoyl is, for example, C_2-C_{10}alkanoyl and is in particular C_2-C_7alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C_2-C_5alkanoyl is preferred.

Haloalkylsulfamoyl is in particular halo-C_1-C_{10}alkanesulfamoyl and is in particular C_2-C_7 alkanesulfamoyl, for example, trifluoromethane-, difluoromethane-, 1,1,2-trifluoroethane- or heptafluoropropanesulfamoyl. Halo-C_1-C_4alkanesulfamoyl is preferred.

Pyrrolyl is, for example, 2- or 3-pyrrolyl. Pyrazolyl is 3- or 4-pyrazolyl. Imidazolyl is 2- or 4-imidazolyl. Triazolyl is, for example, 1,3,5-1H-triazol-2-yl or 1,3,4-triazol-2-yl. Tetrazolyl is, for example, 1,2,3,4-tetrazol-5-yl, furyl is 2- or 3-furyl and

thienyl is 2- or 3-thienyl, while suitable pyridyl is 2-, 3- or 4-pyridyl or corresponding N-oxido-pyridyl.

Alkoxy is, for example, C_1-C_{20}alkoxy, in particular C_1-C_{10}alkoxy. Preferred is C_1-C_7alkoxy.

Substituents of residues as mentioned above and below should preferably not comprise those substituents that interfere with the reactants.

Preferred R is selected from the group consisting of phenyl or of pyridyl each of which is unsubstituted or substituted by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, hydroxyl, hydroxyl-C_1-C_7alkyl, halo-C_1-C_7alkyl such as CF_3, formyl, di-C_1-C_7alkoxy-methyl, and C_2-C_7alkylene-methyl; of C_3-C_7cycloalkyl; of C_3-C_7cycloalkenyl; of biphenylyl that is unsubstituted or substituted by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, hydroxyl, hydroxyl-C_1-C_7alkyl, halo-C_1-C_7alkyl such as CF_3, formyl, di-C_1-C_7alkoxy-methyl, and C_2-C_7alkylene-methyl, for example 4'-C_1-C_4alkyl-biphenyl-2-yl, 4'-hydroxy-C_1-C_4alkyl-biphenyl-2-yl, 4'-halo-C_1-C_4alkyl-biphenyl-2-yl, 4'-formyl-biphenyl-2yl, 4-di- di-C_1-C_4alkoxy-methyl, or C_2-C_5alkylene-methyl; of C_1-C_7alkyl that is unsubstituted or substituted by a substituent selected from the group consisting of halogen, of phenyl; of phenylsulphonyl, of phenylsuphinyl, and of phenylmercapto, phenyl being in each case unsubstituted or substituted by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, hydroxyl, hydroxyl-C_1-C_7alkyl, and halo-C_1-C_7alkyl such as CF_3; of carboxy, and of N-phenyl-N-C_1-C_7alkyl-amino phenyl being in each case unsubstituted or substituted by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, hydroxyl, hydroxyl-C_1-C_7alkyl, and halo-C_1-C_7alkyl such as CF_3; and of C_2-C_7alkenyl that is unsubstituted or substituted by a substituent selected from the group consisting of halogen, of phenyl; of phenylsulphonyl, of phenylsuphinyl, and of phenylmercapto, phenyl being in each case unsubstituted or substituted by a substituent selected from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, hydroxyl, hydroxyl-C_1-C_7alkyl, and halo-C_1-C_7alkyl such as CF_3; of carboxy, and of N-phenyl-N-C_1-C_7alkyl-amino phenyl being in each case unsubstituted or substituted by a substituent selected

from the group consisting of halogen, C_1-C_7alkyl, C_1-C_7alkoxy, hydroxyl, hydroxyl-C_1-C_7alkyl, and halo-C_1-C_7alkyl such as CF_3.

Specifically preferred R is selected from the group consisting of halophenyl such as 2-, 4-chlorophenyl, 2-fluorophenyl; of hydroxyphenyl such as 2-hydroxyphenyl; of CF_3-phenyl such as 2-CF_3-phenyl; of halo-pyridyl such as 2-chloro-5-pyridyl; of hydroxy-pyridyl such as 2-hydroxy-5-pyridyl; of biphenyl that is substituted by C_1-C_4-alkyl, halo-C_1-C_4-alkyl, hydroxyl-C_1-C_4-alkyl, or formyl; of phenyl-C_2-C_4-alkenyl; of 1-carboxy-2-phenyl-C_2-C_4-alkenyl, such as 4'-methyl-biphenyl-2-yl, 4'-bromomethyl-biphenyl-2-yl, 4'-formyl-biphenyl-2-yl, or 4-hydroxymethyl-biphenyl-2-yl; of carboxy-C_1-C_4-alkyl, for example, carboxy-methyl; of phenylsulphonyl-C_1-C-alkyl such as phenylsulphonyl-methyl; of phenylmercapto-C_1-C_4-alkyl such as phenylmercaptomethyl; of C_3-C_6-cycloalkyl such as cyclopropyl or cyclobutyl; of C_3-C_8-cycloalkenyl such as 1-cyclohexenyl; and of N-phenyl-N'-C_1-C_4-alkyl-amino-C_1-C_4-alkyl such as 2-(N-phenyl-N'-methyl-amino)-methyl.

The reactions described above and below in the variants are carried out, for example, in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

Preferably, a compound of formula (II a) is used, wherein substituents of variable R do not interfere during the reaction with a compound of formula (II b).

A compound of formula (II a) is preferably a corresponding compound, wherein R is as defined above.

A preferred azide of formula **$(R_1)(R_2)M$-N_3 (II b)** is a corresponding compound, wherein M is aluminium or boron, R_1 and R_2, independently of one another, is C_1-C_8-alkyl such as methyl, ethyl, propyl, diisobutyl, tert-butyl or n-octyl; C_3-C_7alkenyl such as allyl or crotyl, C_3-C_7-cycloalkyl such as cyclohexyl; phenyl-C_1-C_4-alkyl such as benzyl or 2-phenethyl; phenyl-C_3-

C_5alkenyl such as cinnamyl, or C_3-C_8-cycloalkyl-C_1-C_8-alkyl such as cyclopropylmethyl or cyclohexylmethyl.

Especially preferred azides are those as mentioned in the Examples.

The molar ratio of an azide of formula (II b) and a nitrile of formula (II a) is in a range from 5 to 1, preferably, from 3 to 1, most preferably, from 1,8 to 1 or from 1,2 to 1.

An inert solvent, diluent or mixture thereof should be selected which means that it cannot react with the starting material or intermediates. A suitable solvent is, for example, selected from the group consisting of aliphatic, cycloaliphatic and aromatic hydrocarbon, such as an C_5-C_{10}-alkane e.g. heptane, a halogenated C_5-C_{10}alkane such as 1-chloropentane or 1-chlorohexane, a cycloalkane such as cyclohexane; an alkylated C_3-C_7cycloalkane such as methyl-cyclohexane or 1,3-dimethyl-cyclohexane, an alkylated benzene such as ethylbenzene, toluene, xylene, cumene, or mesitylene; a halogenated aromatic solvent such as chlorobenzene, chlorotoluene, dichlorobenzene, and trifluoromethylbenzene which may be further substituted e.g. by C_1-C_7alkyl or C_1-C_7alkoxy; an a halogenated hydrocarbon, for example, a halogenated aromatic compound, such as chlorobenzene. Furthermore, a suitable solvent, diluent or mixture thereof should have a boiling point that is high enough to be used under the reaction conditions.

Preferred solvents or diluents are aliphatic hydrocarbons, for example, C_6-C_9alkanes such as heptane; aromatic hydrocarbons, for example, phenyl substituted by C_1-C_4alkyl such as toluene or xylene, or mixtures thereof.

The reaction temperature is preferred in the temperature range of from room temperature to the boiling point of the solvent, diluent or mixture thereof, for example, a reaction temperature range is from about 20°C to about 170°C, preferably, from about 60°C to about 130°C, depending on the reactivity and combination of the reactants. A person skilled in the art is fully enabled to select corresponding suitable solvent and diluent systems and reaction conditions adapted to the choice of the solvent system and reactants.

The reaction is most preferably carried out under anhydrous conditions.

In a preferred embodiment of the present invention, the invention is carried out in a temperature range of from 80 to 120°C , preferably between 90 and 110°C.

Compounds of formula (II a) are either known or can be prepared using methods known in the art.

Preferred are compounds of formula (II a), wherein R represents a carbocyclic or heterocyclic residues.

The present invention likewise relates to a compound of formula (II b). Preferred compounds of formula (II b) are those, wherein R_1 and R_2, independently of one another, are C_1-C_{10}alkyl, C_3-C_8alkenyl, C_3-C_8-cycloalkyl, alkylated C_3-C_8-cycloalkyl or ar-C_1-C_5alkyl, especially methyl, ethyl, isopropyl, butyl, isobutyl, octyl, allyl, cyclopropyl, cyclopentyl, cyclohexyl, methyl-cyclohexyl, or benzyl.

Azides of formula (II b) can be prepared, for example, by reacting a compound of formula **$(R_1)(R_2)M$-X (II c)**, wherein M is aluminium or boron, R_1 and R_2 have the meanings as defined about and X is halogen, such as fluoride, chloride, bromide or iodide;or a sulphonate, such as a alkane sulfonate e.g. methanesulphonate; a halogenated alkane sulfonate e.g. trifluoromethansulfonate, an aromatic sulphonate e.g. tosylate; with an alkaline metal azide, such as a lithium, sodium or potassium azide.

The formation of an azide of formula (II b) is carried out, in particular, in the presence of an inert solvent or diluent or a mixture thereof, in a temperature range of 0°C to 120°C. The reaction is most preferably carried out under anhydrous conditions.

Preferred azides comprise compounds of formula (II b), wherein R_1 and R_2, independently of one another, represent C_1-C_8-alkyl such as ethyl, iso-propyl, n-propyl, n-butyl, sec-butyl, tert-butyl or n-octyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_8-alkyl or aryl-C_1-C_8-alkyl such as benzyl or 2 phenethyl; and M is boron or aluminium. Corresponding representatives are dimethyl aluminium azide, diethyl aluminium azide, diisopropyl aluminium azide, dipropyl aluminium azide, diisobutyl aluminium azide, dibutyl aluminium azide, dicyclohexyl aluminium azide, diethyl boron azide, diisopropyl boron azide, dipropyl boron azide, diisobutyl boron

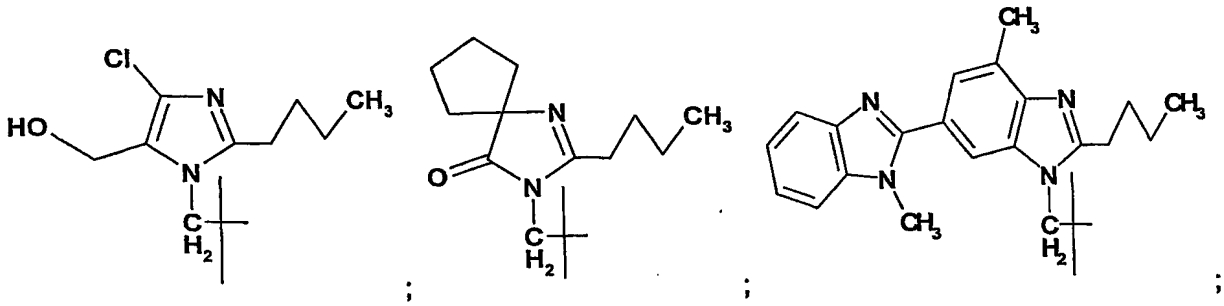
azide, dibutyl boron azide or dicyclohexyl boron azide, furthermore diaryl boron azide such as diphenyl boron azide.

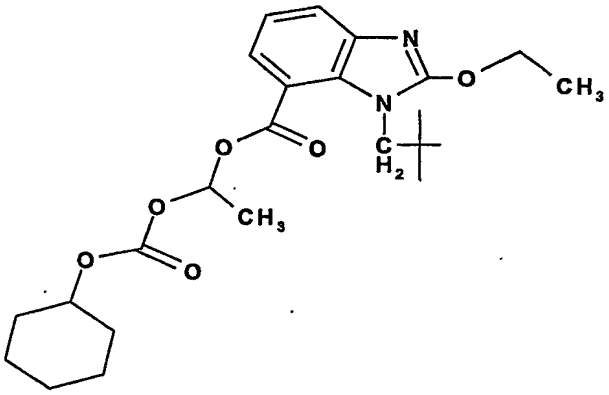
It might be that, dependent on the kind of substiuents, reactive substituents could also react with the azide. For example, an aromatic hydroxy group may react with an azide of formula (II b), however, the resulting organo metal hydroxy function can be split with an acid resulting in a compound of formula (I); accordingly, in this situation, a higher amount of a compound of formula (II a) needs to be used. An ester group might form an acyl-azide with a compound of formula (II b), while an epoxy ring structure might be opened with an compound of formula (II b). However, the person skilled in the art would be able to either directly anticipate that starting compounds with specific reactive substituents could not be used, as these substituents might react with the azide instead of the cyano function, or the person skilled in the art would, when corresponding side reactions are realized, protect corresponding reactive groups and lateron split-off the corresponding protecting groups by using conventional methods known per se.

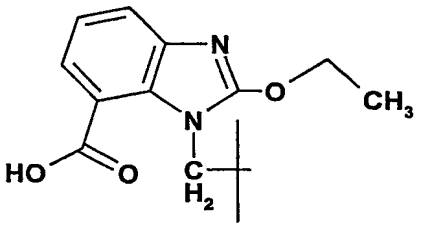
The process of the present invention likewise comprises protecting reactive substituents of compounds of formulae (II a) and (II b) and, after formation of the tetrazole ring, splitting-off the corresponding protective group(s), especially by using conventional methods known per se e.g. by the person skilled in the pertinent art who is familiar with protecting and de-protecting functional groups.

Most angiotensin II receptor antagonists have two essential structural elements, the so-called "core part" and the "pharmacophore".

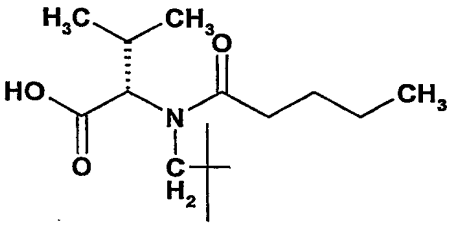
The core part of angiotensin II receptor antagonists comprises, for example, following structural elements:



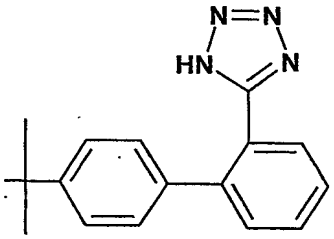




; and



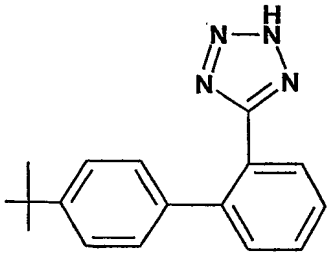
The pharmacophore element of corresponding angiotensin II receptor antagonists is represented by formula



(III a)

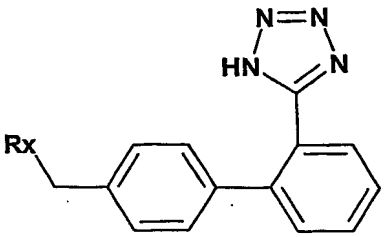
or is a tautomeric form thereof.

A tautomeric form of the side chain of formula (III a) is represented by formula (III b)



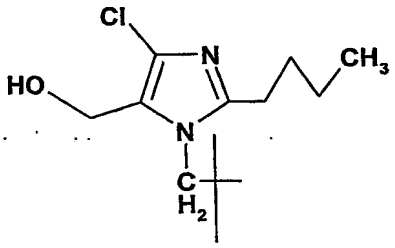
(III b).

The present invention likewise relates to a process for the manufacture of said angiotensin II receptor antagonists having as structural feature a tetrazol ring, e.g. of formula (IV),



(IV)

or a tautomeric form thereof, wherein Rx represents a structural element selected from the group consisting of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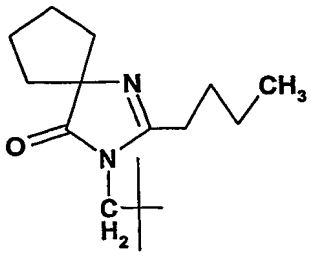
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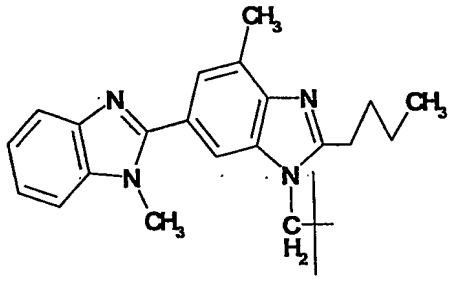
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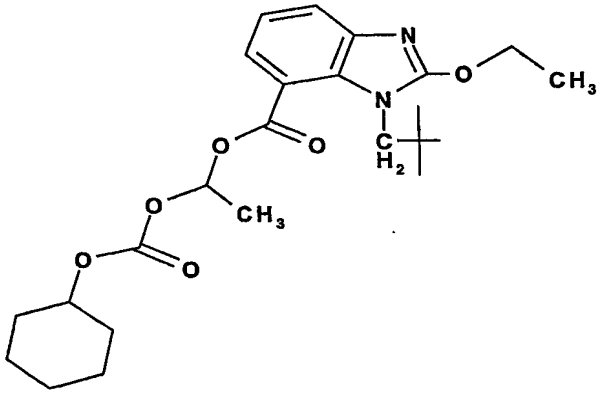
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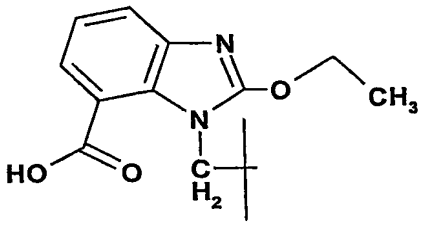
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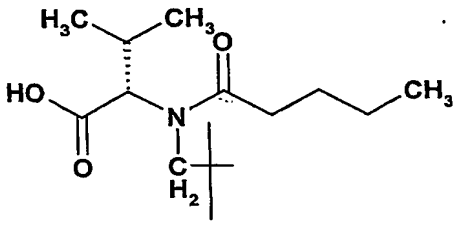
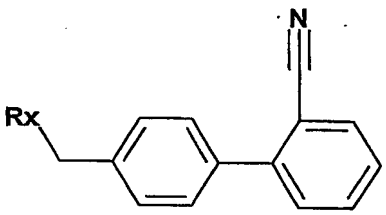


or, in each case, a salt thereof.

This process is characterized by reacting a compound of formula (IV a)

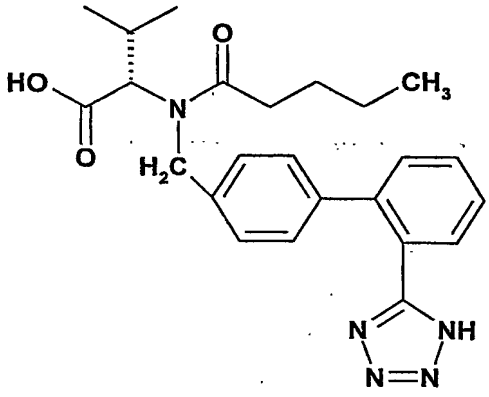


(IV a),

wherein Rx has the meanings as given above,

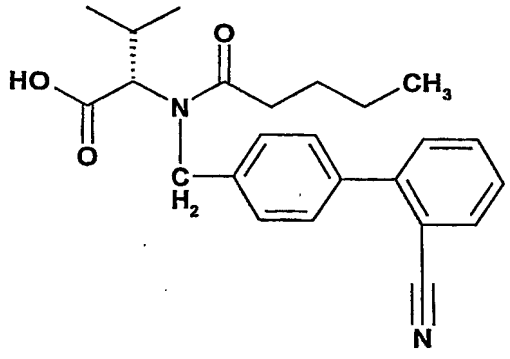
with a compound of formula **$(R_1)(R_2)M\text{-}N_3$ (II b)**, wherein R_1 and R_2, independently of one another, represent an organic residue; and isolating the resulting compound of formula (IV).

A preferred angiotensin II receptor antagonist is the compound of formula



(IV b).

A preferred variant of the process according to the present invention for the manufacture of a compound of formula (IV b) is characterized by reacting a compound of formula (IV c)

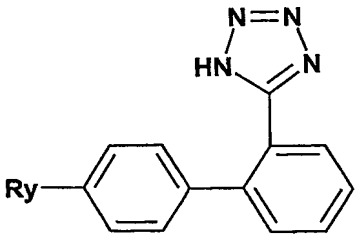


(IV c)

or an ester thereof with an azide of formula $(R_1)(R_2)M\text{-}N_3$ (IIb), wherein R_1 and R_2, independently of each other, have the meanings as defined above, and isolating the compound of formula (IV b).

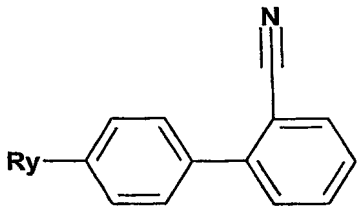
An ester of a compound of formula (IV c) is, for example, an ester derived from an aliphatic, araliphatic, cycloaliphatic, cycloaliphatic-aliphatic or aromatic alcohol. Preferred is a C_1-C_7-alkyl ester or a aryl-C_1-C_2-alkyl ester, most preferred a benzylester thereof.

A preferred embodiment of the present invention is a process for the manufacture of a compound of formula



(V)

a tautomeric form thereof wherein Ry represents C_1-C_8-alkyl such as methyl; C_1-C_8-alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, formyl or an acetal thereof; comprising reacting a compound of formula (IV a)



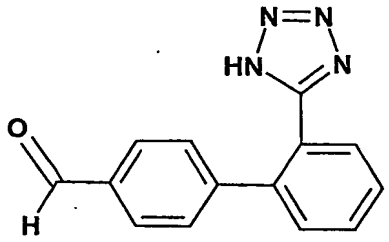
(V a)

with a compound of formula **$(R_1)(R_2)M$-N_3 (II b)**, wherein R_1 and R_2, independently of one another, represent an organic residue; and isolating the resulting compound of formula (V).

An acetal of a formyl group is, for example, the corresponding di-C_1-C_8alkoxymethyl such as dimethoxy- or diethoxy-methyl, or methylene-oxy-C_2-C_6-alkylene-oxy such as methyleneoxy-ethyleneoxy.

The present invention likewise relates to the above reaction. Furthermore, the present invention relates to the compounds of formula (VI) or a tautomer or a salt thereof in a form being completely free of tin. The present invention also relates to compounds of formula (VI) whenever obtained according to above reaction.

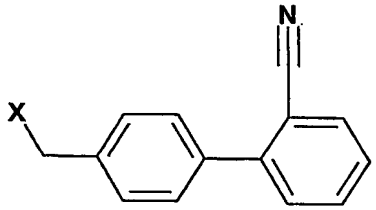
A variant of the process for the manufacture of the compound of formula (V) is a process for the manufacture of a compound of formula (VI)



(VI)

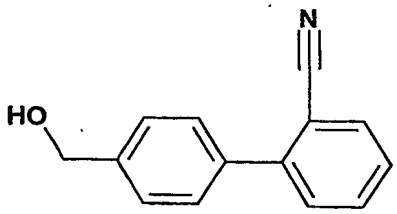
or a tautomer or salt thereof, comprising

(a) treating a compound of formula (VI a)



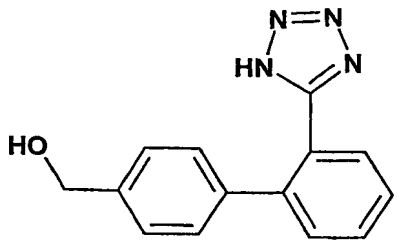
(VI a),

wherein X represents a leaving group, first with a nucleophilic agent and then with a "solvolytic" base resulting in a compound of formula (VI b)



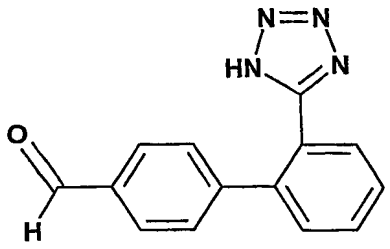
(VI b);

(b) reacting a compound of formula (V b) with an azide of formula **$(R_1)(R_2)M\text{-}N_3$ (II b)**, wherein the variables R_1 and R_2, independently of one another, have the meanings as defined above; resulting in a compound of formula (VI c)



(VI c) or a tautomer or salt thereof

(c) oxidizing a compound of formula (V c) or a tautomer or salt thereof resulting in a compound of formula (V)



(V d)

or a tautomer or salt thereof; and

(d) isolating the compound of formula (IV b) or a tautomer or salt thereof.

The present invention relates to each of reaction steps (a) to (c) and to the product obtained according to the complete reaction sequence, but also according to each of reaction steps (a) to (c).

The reactions described above and below in the variants are carried out in a manner known per se, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions.

Step (a) is carried out, for example, in the presence of a base, e.g. first a nucleophilic agent followed by treatment with a saponifying base.

A suitable nucleophilic agent is, for example, an alkaline metal salt of a C_2-C_{10}-alkanecarboxylic acid, especially of a C_2-C_5-alkanecarboxylic acid, an araliphatic carboxylcic acid or an aromatic carboxylic acid, or aliphatic ammonium hydroxides, especially tetra-C_1-C_7-alkyl-ammonium hydroxides. Examples comprise e.g. lithium acetate, sodium acetate, potassium acetate, and tetraethylammonium hydroxide.

Suitable saponifying bases are, for example, alkali metal hydroxides, hydrides, amides, alkanolates, carbonates, triphenylmethylides, di-lower alkylamides, aminoalkylamides or lower alkylsilylamides, naphthaleneamines, lower alkylamines, basic heterocycles, ammonium hydroxides, and carbocyclic amines. Examples which may be mentioned are sodium hydroxide, sodium hydride,

sodium amide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium carbonate, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU), the last two bases preferably in the presence of water.

Likewise, in a specially preferred embodiment Step (a) is carried out in the presence of a phase transfer catalyst, for example, those known in the art. Suitable phase transfer catalysts comprise tri-C_1-C_8-alkyl-ar-C_1-C_5alkyl-ammonium halides such as corresponding chlorides or bromides, tetra-C_1-C_8-alkyl-ammonium halides such as corresponding chlorides or bromides, di-C_1-C_8-alkyl-diar-C_1-C_5alkyl-ammonium halides such as corresponding chlorides or bromides. Examples are tetrabutyl ammonium bromide or triethylbenzylammonium chloride.

More than one mol equivalent of a base is normally used, preferably from 1.1 to 1.5 equivalents.

An inert solvent or a mixture of solvents is used. Suitable solvents comprise e.g. hydrocarbons such as heptane, toluene or xylene, a halogenated hydrocarbons such as methylenechloride, 1,2-dichloroethane, chlorobenzene, fluorobenzene or trifluorobenzene.

The reaction temperature is, for example, from 0°C to the boiling point of the solvent, preferably from 0°C to 130°C, more preferably from 40°C to 80°C.

The present invention relates to the reaction Step (a). This reaction step comprises two separate steps and it is suprising that the yield is nearly quantitative (> 99% by weight theory). The present invention also relates to compounds of formula (VI b) whenever obtained according to process Step (a).

Step (b): The molar ratio of an azide of formula (II b) and a nitrile of formula (VI b) is in a range from 5 to 1, preferably, from 3 to 1, most preferably, from 1,8 to 1 or from 1,2 to 1.

An inert solvent, diluent or mixture thereof should be selected which means that it cannot react with the starting material or intermediates. A suitable solvent is, for example, selected from the group consisting of aliphatic, cycloaliphatic and aromatic hydrocarbon, such as an

C_5-C_{10}-alkane e.g. heptane, a halogenated C_5-C_{10}alkane such as 1-chloropentane or 1-chlorohexane, a cycloalkane such as cyclohexane; an alkylated C_3-C_7cycloalkane such as methyl-cyclohexane or 1,3-dimethyl-cyclohexane, an alkylated benzene such as ethylbenzene, toluene, xylene, cumene, or mesitylene; a halogenated aromatic solvent such as chlorobenzene, chlorotoluene, dichlorobenzene, and trifluoromethylbenzene; a halogenated hydrocarbon, for example, a halogenated aromatic compound, such as chlorobenzene. Furthermore, a suitable solvent, diluent or mixture thereof should have a boiling point that is high enough to be used under the reaction conditions.

Preferred solvents or diluents are aliphatic hydrocarbons, for example, C_6-C_9alkanes such as heptane; aromatic hydrocarbons, for example, phenyl substituted by C_1-C_4alkyl such as toluene or xylene, or mixtures thereof.

The reaction temperature is preferred in the temperature range of from room temperature to the boiling point of the solvent, diluent or mixture thereof, for example, a reaction temperature range is from about 20°C to about 170°C, preferably, from about 60°C to about 130°C, depending on the reactivity and combination of the reactants. A person skilled in the art is fully enabled to select corresponding suitable solvent and diluent systems and reaction conditions adapted to the choice of the solvent system and reactants.

The reaction is most preferably carried out under anhydrous conditions.

In a preferred embodiment of the present invention, the invention is carried out in a temperature range of from 80 to 120°C , preferably between 90 and 110°C.

The present invention likewise relates to reaction Step (b). Furthermore, the present invention relates to the compounds of formula (VI c) or a tautomer or a salt thereof in a form being completely free of tin. The present invention also relates to compounds of formula (VI c) whenever obtained according to process Step (b).

Step (c): The oxidation is carried out in the presence of a suitable oxidizing agent. A suitable oxidizing agent is for example, an alkali metal hypochlorite such as lithium or sodium or potassium hypochlorite, a tempo or an analogue (cf. Fluka) thereof or an oxidizing

agent selected from the group consisting of HNO_2, HNO_3 or corresponding anhydrides thereof, and peroxodisulfates.

When using e.g. an alkali metal hypochlorite as oxidizing agent, the oxidation is carried out, for example, in an inert solvent, e.g. a sovent that is inert against oxidation, such as a lower alkanecarboxylic acid, for example acetic acid, a heterocyclic aromatic, for example pyridine, a halogenated hydrocarbon, or water or a mixture thereof, if necessary with cooling or warming, for example from about 0° to about 50°C, for example, at room temperature. In a preferred variant, the reaction is carried out in an aqueous medium and in the presence of a base. A suitable base is, among others, an alkaline carbonate, such as potassium carbonate.

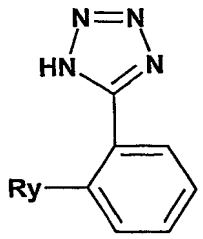
When using oxidizing agents such as HNO_2, HNO_3 or corresponding anhydrides thereof, or peroxodisulfates, especially nitric acid, in a preferred variant an alkylated aromatic hydrocarbon such as toluene or xylene may be used as solvent. In a preferred variant of the oxidization with as HNO_2, HNO_3 or corresponding anhydrides thereof, or peroxodisulfates, the reaction is preferably carried out in a temperature range from about 0°C to room temperature. Surprisingly, no oxidation of the solvent is observed; i.e. the methyl groups in toluene or xylene are resistant to oxidation. Accordingly, the use of oxidizing agents such as HNO_2, HNO_3 or corresponding anhydrides thereof, or peroxodisulfates is likewise a subject matter of the present invention as is reaction Step c), especially when using as oxidizing agents such as HNO_2, HNO_3 or corresponding anhydrides thereof, or peroxodisulfates in the an alkylated aromatic hydrocarbon solvent, especially in toluene and xylene. In another preferred variant, HNO_3 is used in water free form or in an aqueous solution from about 40% to about 95%, preferably from 40 to 65 %.

The use of oxidizing agents such as HNO_2, HNO_3 or corresponding anhydrides thereof, or peroxodisulfates, especially nitric acid, provides surprising results. For example, the corresponding oxidization to an aldehyde is effected without further oxidizing the aldehyde function to the carboxy group. Accordingly, the use of said oxidizing agents is likewise a subject matter of the present invention.

The present invention also relates to compounds of formula (VI) whenever obtained according to process Step (c).

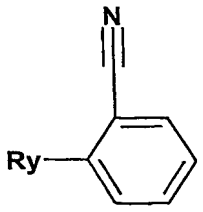
Step (d): The isolation step of a compound of formula (VI) is carried out according to conventional isolation methods, such as by crystallizing the resulting compound of formula (VI) from the reaction mixture – if desired or necessary after work-up, especially by extraction - or by chromatography of the reaction mixture.

A further preferred embodiment of the present invention is a process for the manufacture of a compound of formula



(VII)

a tautomeric form thereof, wherein Ry represents C_1-C_8-alkyl such as methyl; C_1-C_8-alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, formyl or an acetal thereof; comprising reacting a compound of formula (VII a)



(VII a)

with a compound of formula **$(R_1)(R_2)M$-N_3 (II b)**, wherein R_1 and R_2, independently of one another, represent an organic residue; and isolating the resulting compound of formula (VI).

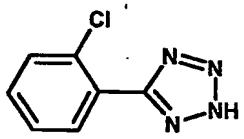
The present invention likewise relates to the above reaction. Furthermore, the present invention relates to the compounds of formula (VII) or a tautomer or a salt thereof in a form being completely free of tin. The present invention also relates to compounds of formula (VII) whenever obtained according to above reaction.

The isolation step of a compound of formulae (VI) or (VII), respectively, is carried out according to conventional isolation methods, such as by crystallizing the resulting compound of formula (VI)) or (VII), respectively, from the reaction mixture or by chromatography of the reaction mixture.

The conversion of an acid into a salt is carried out in a manner known per se. Thus, for example, a salt with a base is obtained by treating the acid form with a base. Salts with a base can, on the other hand, be converted into the acid (free compound) in a customary manner, and salts with a base can be converted, for example, by treating with a suitable acid agent.

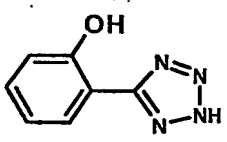
The invention relates to the compounds obtained according any process of the present invention.

Example 1: 5-(2-Chlorophenyl)-1H-tetrazole



20 mmol (1.3 g) of sodium azide are charged to 25 ml flask under argon atmosphere followed by slow addition (via syringe) of 11 ml of a solution of diethyl aluminium chloride (1.8 molar in toluene), 20 mmol, at 0 °C under stirring. The suspension is stirred over night at room temperature. Then 2.06 g (15 mmol) solid 2-chloro-benzonitrile are added and the mixture is heated at external temperature of 90 °C for 9 hours. After this time the conversion was 91.5 % (HPLC). For complete conversion
(> 99.5 %, HPLC) the reaction mixture is kept for additional 6 hours at 90 °C. For work up the reaction mixture was quenched at 0 °C under stirring on 20 ml HCl (6N) which contains 2.6 g of $NaNO_2$ to destroy excess hydrazoic acid. The thick white precipitate which is formed (product) is stirred at 0 °C for additional 1 hour and then filtered and dried over night at 50 °C to give the white crystalline product.
m.p. 173 - 175 °C
Tlc: R_f-value: 0.48, toluene : EtOAc : AcOH (20 : 20 : 1); SiO_2 -plates.

Example 2: 5-(2-Hydroxyphenyl)-1H-tetrazole



Method A:

286 mg of granular sodium azide (4.4 mmol) are added to a cold solution of diethyl aluminium chloride (4.4 mmol, 1M in toluene) and the mixture is stirred at room temperature for 4 hours (h). A solution of 2-hydroxybenzonitrile (4 mmol, 476 mg) in 3 ml of toluene, cooled at 0°C, is treated with 2.2 ml of triethyl aluminium (4 mmol, 1.8 M in toluene). The mixture reaction is warmed to room temperature and stirred for 1 hour. The mixture is cooled to 0°C, treated with the solution of diethyl aluminium azide, gradually warmed to 85°C and stirred over two days. The reaction mixture is cooled to -10°C and treated drop wise with 7 ml of HCl 6 N. 10 ml of ethyl acetate are added and the mixture is extracted once with 10 ml of water, once with 10 ml of NaCl saturated. The combined aqueous layers are extracted three times with 10 ml of ethyl acetate. The combined organic phases are dried over Na_2SO_4. The solvent is removed to give the crude product.

Method B:

260 mg of granular sodium azide (4 mmol) is added to a cold solution of diethyl aluminium chloride (4 mmol, 1.8 M in toluene) diluted with 10 ml of toluene, and the mixture is stirred at room temperature for 4 hours. The stirred solution is cooled at 0°C and 238 mg of 2-hydroxybenzonitrile (2 mmol) are added. The mixture reaction is warmed to 80°C and stirred over night. After 20 hours the conversions was 83 %. Then the temperature is increased to 100°C and stirred 12 hours. At a conversion of around 90% the reaction is worked up. The reaction mixture is cooled to 0°C and treated drop wise with 7 ml of HCl 6 M, 5 ml of water, 10 ml of ethyl acetate, 8 ml of saturated NaCl (sat.) and extracted. The organic phase is reextracted twice with 20 ml of water. The combining aqueous layers are extracted twice with 20 ml of ethyl acetate. The combining organic phases are dried over Na_2SO_4. The solvent is removed to give the crude product. The crude product is crystallized from ethyl acetate to give the pure product.

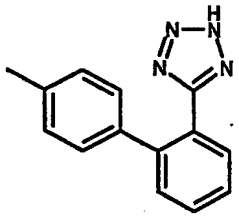
m.p.: 220 – 222 ° C,

Tlc: Rf – value: 0.46, toluene : EtOAc : AcOH (20 : 20 : 1).

HPLC:

Hewlett Packard, solvents. H_3PO4, acetonitrile/water; flow: 2 ml/min; injection: 5.0 µl; wavelength 220 nm, 40 °C. Column: Merck, Chromolith Performance, RP-18e 100-4.6 mm; Ret. Time: 4.12 min.

Example 3a: 5-(4'-methylbiphenyl-2-yl)-1H-tetrazole



A 20 ml flask is dried under argon and then charged with 7 ml of diisobutylaluminium fluoride (1 molar in hexane) followed by 5 ml of toluene and 455 mg of NaN_3 (7 mmol). After stirring the suspension for 4 hours at room temperature 966 mg of solid ortho-tolylbenzonitrile is added at 0 ° C in one portion. The suspension is warmed up to 130 °C (ext. temp.) with an internal temperature of 100 °C. After 3 h the conversion is 31.5 %. After 44 h at 130 °C (ext. temp.) the conversion is > 93 %. The reaction mixture was quenched in hydrochloric acid (6 molar). After addition of 10 ml of toluene the layers are separated, the organic layer is washed twice with 20 ml of water, dried over sodium sulfate and evaporated to give a crystalline residue (900 mg, 76 %) of the product.
Physicochemical data see example 3b.

Example 3b: 5-(4'-methylbiphenyl-2-yl)-1H-tetrazole

Same reaction as in example 3a was carried out, but with diethylaluminium azide at higher concentration and higher temperatur:

Under similar conditions with diethylaluminium azide (prepared from diethylaluminium chloride and NaN_3) in toluene and OTBN a conversion of 98.5 % was obtained after 40 hours at internal temperature of ca. 110 °C (reflux), external temperatur 135 °C.

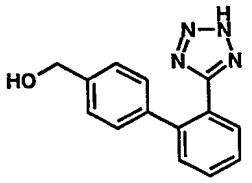
A dry 50 ml flask is charged with 5 ml toluene and 1.3 g (20 mmol) of dry solid sodium azide. The stirred suspension is cooled to 0 °C and 11 ml of a 1.8 molar solution of diethylaluminium chloride (20 mmol) is added via syringe during 10 minutes. The suspension is stirred for 4 to 6 hours or over night at room temperature. Then the suspension is cooled to 0 °C and a solution of o-tolylbenzonitrile (2.1 g, 11 mmol) in 5 ml toluene is added dropwise during 5 minutes. The stirred suspensiun is heated up to reflux and after 7 hours a conversion of 54.5 % (HPLC) is obtained. After refluxing over night (17 h) a conversion of 92 % is observed. After 40 h the conversion is > 98.5 %. Thereafter the reaction is quenched by droping the reaction mixture to cold 2 N hydrochloric acid (50 ml) under stirring to give a

white precipitate which is dissolved by addition of 20 ml of acetonitrile to give a clear biphasic solution. The product is extracted with 50 ml of isopropyl acetate. The organic phase is treated with aqueous pottasium carbonate solution (pH 10) until all product is dissolved in the aqueous layer as the pottasium salt. Then the basic aqueous phase is adjusted to pH 1-2 by addition of ca. 90 ml of 2N HCl. The product is extracted twice with 50 ml of isopropyl acetate and the organic phase is evaporated under reduced pressure to give after drying in vacuum the very pure, white crystalline product.

m.p.: 150 – 152 ° C; (Ref. substance: DiPharma sample: m.p. 149-151 °C)

Tlc: R_f -value: 0.56, (Toluene : EtOAc : AcOH = 20 : 20 : 1), SiO_2-plate (Merck KgaA)

Example 4 a: 5-(4'-Hydroxymethylbiphenyl-2-yl)-1H-tetrazole



[2'-(2H-Tetrazol-5-yl)-biphenyl-4-yl]-methanol

1.235 g of granular sodium azide (19 mmol) are added to a cold solution of diisobutyl aluminium chloride (19 mmol, 1.8M in toluene) diluted in 5 ml of toluene and the mixture is stirred at room temperature over the night to give diisobutyl aluminium azide. 2.1 g of 4'-hydroxymethyl-biphenyl-2-carbonitrile (10 mmol), are treated, in a drop wise manner at 0 °C with 5.52 ml of triethyl aluminium (10 mmol; 1.8M in toluene). The reaction mixture is stirred for 5 minutes. After that, the clear colourless reaction mixture is added to the solution of diisobutyl aluminium azide (19 mmol), gradually warmed to an internal temperature of about 100°C and stirred over the night (conversion 95.7%). For the work up the reaction mixture is cooled to 0°C and added dropwise to a solution of 30 ml of HCl (2 N) containing 1.38g of $NaNO_2$ (20 mmol) (cooled to 0°C). 40 ml of iso-propyl acetate are added and the mixture is extracted once with 15 ml of HCl 2N, once with 20 ml of water. The combining aqueous layers are extracted twice with 10 ml of isopropyl acetate. The organic phase is extracted three times with 15 ml portions of an aqueous solution of K_2CO_3 (10%). The aqueous phase is washed once with 15 ml of isopropyl acetate. HCl (2 N) is added to the aqueous phase to adjust the pH to 2, and the solution is extracted three times with 20 ml portion of isopropyl

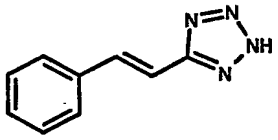
acetate. The combining organic phase is washed once with 20 ml of water and the solvent is removed to give the crude product. The crude product is crystallized from ethyl acetate and isopropyl ether to give the pure product.

m.p.: 137 – 139 ° C;

Tlc: Rf-value: 0.21, (toluene : EtOAc : AcOH = 20 : 20 : 1), SiO_2 - plates (Merck KgaA) Catalog -Nr. 1.05628.0001)

Example 4 b: The reaction as in Example can also be carried out with diethyl aluminium azide at higher concentration and higher temperature.

Example 5: Synthesis of 5-((E)-Styryl-2H-tetrazole



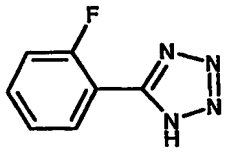
Procedure:

To a 50 ml, three necked round bottomed flask, 10 ml of a solution of diisobutyl aluminium fluoride (10 mmol, 1 M in hexane), diluted in 10 ml of toluene, are added. NaN_3 is added to the solution (650 mg, 10 mmol), and the mixture is stirred at room temperature for 4h. The stirred solution is cooled at 0°C with an ice-bath. 0.62 ml of cinnamonitrile (5 mmol) diluted in 3 ml of toluene are added, the mixture is warmed to 90°C (i.t.) and stirred over the night. The temperature is increased to 105°C (i.t.) and stirred over the night. After a total time of 70 hours (no complete conversion) the reaction was quenched. The mixture is cooled to -10°C and treated drop wise with 8 ml of HCl (6N) (pH1). The aqueous phase is extracted with 10 ml of ethyl acetate. The organic phase is washed twice with 10 ml portion of NaCl sat. and then extracted twice with 10 ml portion of $KHCO_3$. The water phase is washed twice with 10 ml portion of ethyl acetate and then treated with HCl to pH 1-2 and extracted three times with ethyl acetate. The organic phase is dried over Na_2SO_4 and the solvent removed in vacuum to give after drying the title product.

m.p.: 158 – 160 °C

Tlc: Rf-value: 0.46 (Toluene : EtOAc : AcOH (20 : 20 :1)

Example 6: 5-(2-Fluorophenyl)-1H-tetrazole,

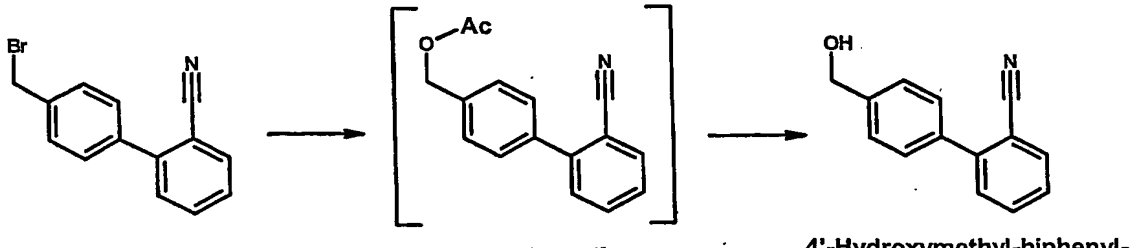


20 mmol (1.3 g) of sodium azide are charged to a 25 ml flask under argon atmosphere followed by slow addition (via syringe) of 11 ml of a solution of diethyl aluminium chloride (1.8 molar in toluene), 20 mmol, at 0 °C under stirring. The suspension is stirred over night. at room temperature. Then 1.8 g (1.2 ml), (15 mmol), 2-fluoro-benzonitrile are added and the mixture is heated at external temperature of 90 °C for 7 hours. After this time the conversion was complete (HPLC). Work up: The reaction mixture is quenched on 20 ml HCl (2 molar) containing 20 mmol $NaNO_2$ at 0 °C to destroy hydrazoic acid which is formed from excess azide. The precipitate which is formed is dissolved by addition of 20 ml acetonitrile to give a clear biphasic solution. The aqueous phase is extracted twice with each 10 ml ethyl acetate. The combined organic phases are extracted with 15 ml of an aqueous solution (10 %) of potassium carbonate and adjusted to pH 10. The organic phase is extracted twice with 10 ml of water. The combined aqueous basic phases are neutralized with 2 N HCl and the pH is adjusted to pH 1-2. The product is extracted with ethyl acetate. The ethyl acetate is evaporated under reduced pressure to give a crystalline residue which is further dried in vacuo at 50 °C to give a white crystalline solid.

m.p.: 158 – 160 °C.

Tlc: Rf –value: 0.48 (toluene : EtOAc : AcOH = 20 : 20 : 1), SiO_2 - plates

Example 7: 4'-Hydroxymethyl-biphenyl-2-carbonitrile



OAc - derivative

4'-Hydroxymethyl-biphenyl-2-carbonitrile

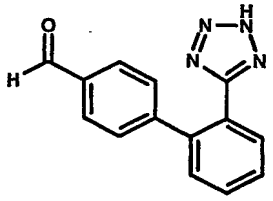
One pot PTC preparation of 4'-Hydroxymethyl-biphenyl-2-carbonitrile from 4'-bromomethyl-biphenyl-2-carbonitrile without isolation of the intermediate OAc derivative.

A 750 ml flask is charged with 54.4 g (0.2 mol) of 4'-bromomethyl-biphenyl-2-carbonitrile and 250 ml of toluene. To this suspension is added a solution of 30 g (0.3 mol) of potassium acetate in 15 ml of water. The heterogeneous mixture is heated up to an internal temperature of 90 ° C to become a clear biphasic solution. After 12 hours at an internal temperature of 90 °C the conversion to the OAc derivative is complete. The biphasic mixture is cooled down to internal temperature of about 50 °C followed by addition of 150 ml NaOH (2N). The mixture is heated up to an internal temperature of ca. 70 °C (extern. temp. 80 °C). After 5 hours at this temperature the PTC saponification is complete (100 % conversion, HPLC). Additional 150 ml toluene is added and the warm reaction solution (ca. 50 °C) is washed three times with 50 ml of hot water until the pH is around 7. The toluene phase is evaporated under reduced pressure and the resulting crystalline residue is dried at 50 °C over 24 hours in vacuum to give the white crystalline product with 98 % purity (HPLC) and a water content of 0.23 %.

m.p.: 118-120 °C

Tlc: : Rf –value: 0.45, (toluene : EtOAc : AcOH = 20 : 20 : 1), SiO_2 - plate

Example 8 a: 5-(4'-Formyl-biphenyl-2-yl)-1H-tetrazole or
2'-(2H-Tetrazol-5-yl)-biphenyl-4-carbaldehyd



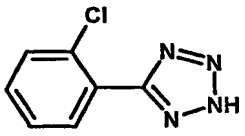
1.01 g (4 mmol) of 5-(4'-hydroxymethylbiphenyl-2-yl)-1H-tetrazole is dissolved in 7 ml of a 10 % aqueous solution of potassium carbonate. To the stirred solution is added an aqueous solution (ca. 8 %) of sodium hypochlorite (eau de Labarraque) at room temperature. After 40 min. a conversion of 50 % to the aldehyde is observed. After 3.5 hours additional 1.5 ml sodium hypochlorite is added at room temperature. After a total reaction time of 7 hours a conversion of > 93 % is observed. Stirring over night at 0 °C improves the conversion to 97 %. The reaction mixture is quenched with 20 % aqueous sodium hydrogen sulfite solution (5 ml) under stirring for 1 hour to destroy excess hypochlorite. Then 2-methyl-2-butene (1.5 ml) is added and the product is precipitated by carefully dropping 10 ml of 6 N HCl at 0 °C to the mixture under stirring. The product is extracted with ethyl acetate and the solvent is evaporated to dryness to give the solid product.

m.p.: 184 – 186 °C

Tlc: Rf –value: 0.41, (toluene : EtOAc : AcOH = 20 : 20 : 1), SiO_2 – plate.

Example 8 b: Compound (Vc), 5-(4'-hydroxymethylbiphenyl-2-yl)-1H-tetrazole, 504 mg (2 mmol) is suspended in a mixture of 2 ml of toluene and 1 ml of dichloromethane. The suspension is cooled to 0 °C and 0.42 ml of nitric acid (ca. 6 mmol), (65 %, d = 1.4) is added in one portion at 0 °C under stirring which results in a clear slightly yellow solution. The ice bath is removed and stirring is continued at room temperature for ca. 1 h. After 1 h the product (Vd) is crystallizing directly from the reaction mixture. The slurry is cooled to 0 °C for 1 h and then filtered to give after drying in vacuum 400 mg of pure aldehyde (Vd).

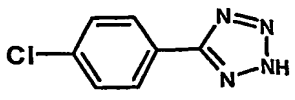
Example 9: 5-(2-Chlorophenyl)-1H-tetrazole (with dibutylboron azide)



A dry 25 ml flask is charged with 10 ml (10 mmol) of a heptane solution of dibutyl boryl triflate (1 molar) under Argon. To this solution is added 650 mg (10 mmol) of sodium azide. The suspension is stirred over night at room temperature to give a dibutylboron azide. To the suspension is added 1.0 g (7.7 mmol) 2-chlorobenzo nitrile as a solid in one portion. The reaction mixture is heated up to 130 ° C external temperature. After 5 hours the conversion to the desired product is only 5 %. Additional 5 ml of toluene is added and refluxing is continued over night. After 24 hours the conversion is 27 %. After additional 24 h refluxing at 130 ° C (ext. temp.) the conversion is 35 % (HPLC). The reaction is stopped by carefully quenching the yellow suspension on 6 N HCl. The product is extracted to the water phase with 2 x 10 ml of potassium carbonate solution. The water layer is adjusted to pH 1 with 6N HCl and the product is extracted with ethyl acetate. The solvent is evaporated to dryness to give an off-white solid residue.

Tlc: R_f-value: 0.48, toluene : EtOAc : AcOH (20 : 20 : 1); SiO_2 -plate.

Example 10: 5-(4-Chlorophenyl)-1H-tetrazole



Procedure:

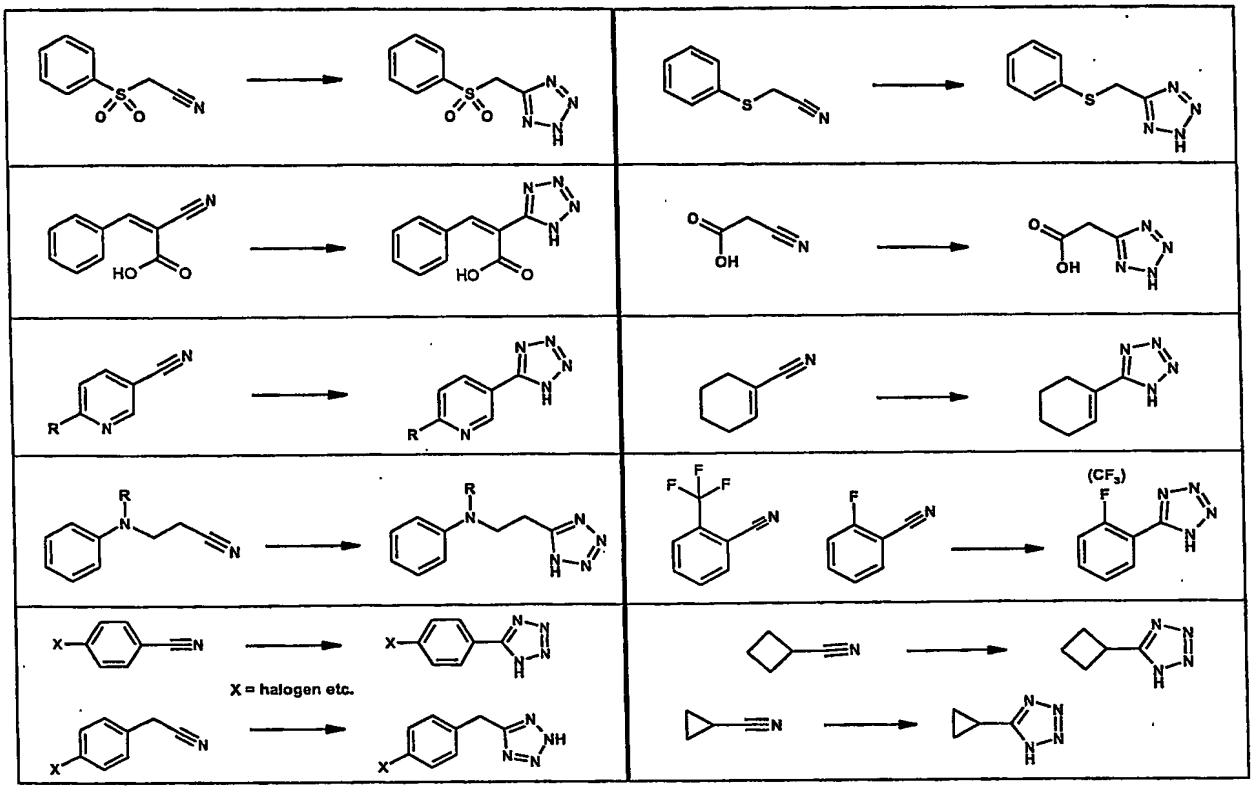
292 mg of granular sodium azide (4.5 mmol) are added to a cold solution of diethyl aluminum chloride (4.5 mmol, 1.8 M in toluene) diluted in 2.5 ml of toluene, and the mixture is stirred at room temperature for 4h. 473 mg of 4-Chlorobenzonitrile are added to the stirred solution, and the reaction mixture is heated up to 135°C (e.t.) and stirred over the night. Complete conversion is observed by HPLC. 5 ml of toluene are added to the mixture, then the solution is added drop wise to a cold solution of HCl 6N. 10 ml of ethyl acetate are added and the solution extracted. The aqueous phase is washed twice with 10 ml portion of ethyl acetate. The combined organic phases are washed with 10 ml portion of HCl 2N and finally with 10 ml of water. The solvent is removed and the product is dried in vacuum at 60°C over the night to give the product.

m.p.: 255 – 257 °C

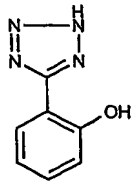
Tlc: R_f-value: 0.40, toluene : EtOAc : AcOH (20 : 20 : 1); SiO_2 -plate.

HPLC: Hewlett Packard, solvents. H_3PO_4, acetonitrile/water; flow: 2 ml/min; injection: 5.0 µl; wavelength 220 nm, 40 °C; flow: 2 ml/min; injection: 5.0 µl; Column: *Merck, Chromolith Performance RP-18e 100-4.6 mm.* Rt. Time: 6.184 min

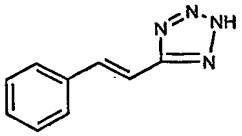
The following table should further illustrate the present invention. When applying the method of the present invention, tetrazole compounds of formula (I) are obtainable starting from nitrile compounds of formula (II a):



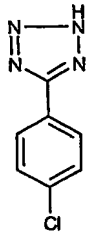
Using the technology as described above, especially as described in the examples, following compounds can be obtained:



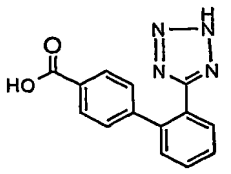
m.p. 220-222°C -



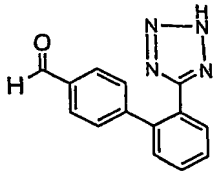
m.p. 158-160°C -



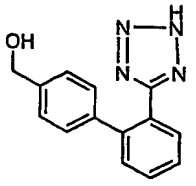
m.p. 255-257°C



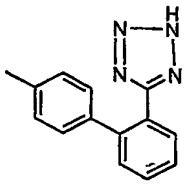
m.p. 253-255°C -



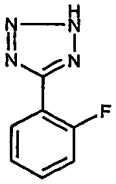
Rf: 0.31



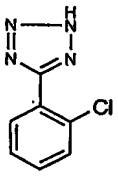
m.p. 140-141°C -



m.p. 150-152°C



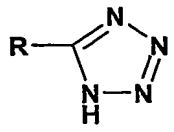
m.p. 158-160°C -



173-175°C

What is claimed is

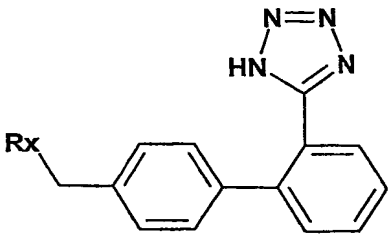
1. A process for the manufacture of a tetrazole of formula



(I)

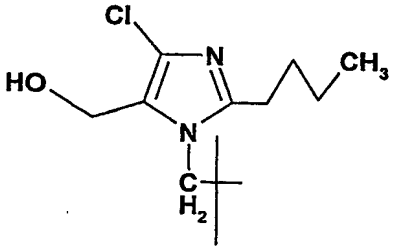
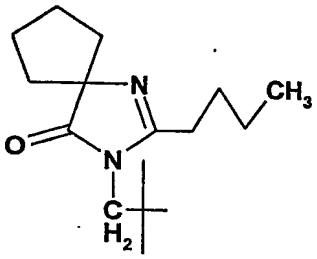
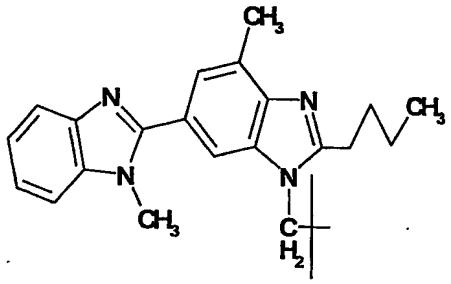
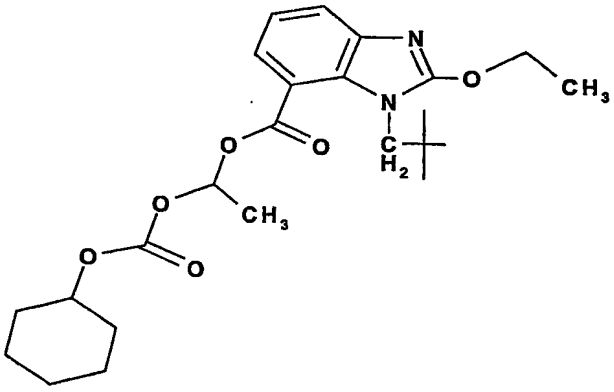
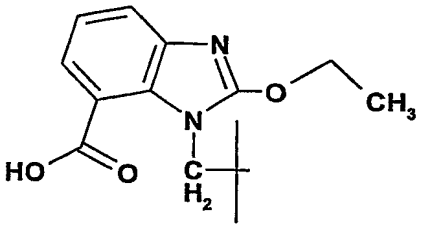
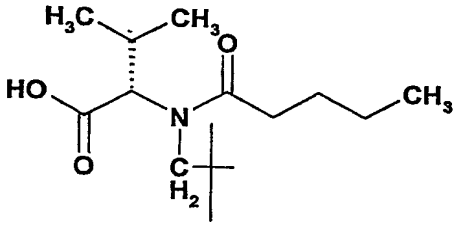
or a tautomer or a salt thereof, wherein R represents an organic residue;
comprising
(i) reacting a compound of formula **R-CN (II a)** with an azide of formula **$(R_1)(R_2)M\text{-}N_3$ (IIb)**, wherein R has the meaning as defined above; R_1 and R_2, independently of another, represent an organic residue such as an aliphatic residue, an alicyclic residue, a heteroalicyclic residue; an alicyclic-aliphatic residue; a heteroalicyclic-aliphatic residue; a carbocyclic or a heterocyclic aromatic residue; an araliphatic residue or an heteroaraliphatic residue, each residue, independently of another, being unsubstituted or substituted; and M is boron or aluminium; and
(ii) isolating the resulting compound of formula (I).

2. A process according to claim 1 for the manufacture of said angiotensin II receptor antagonists having as structural feature a tetrazol ring, e.g. of formula (IV),

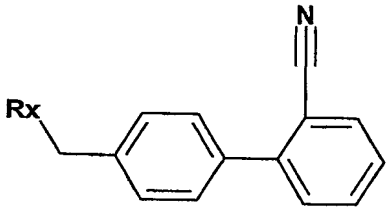


(IV)

or a tautomeric form thereof, wherein Rx represents a structural element selected from the group consisting of

or, in each case, a salt thereof, comprising reacting a compound of formula (IV a)

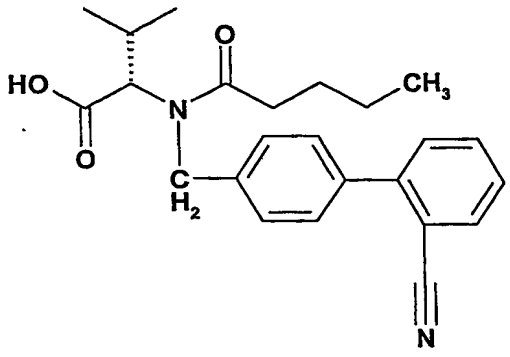


(IV a),

wherein Rx has the meanings as given above,

with a compound of formula **$(R_1)(R_2)M\text{-}N_3$ (II b)**, wherein R_1 and R_2, independently of one another, represent an organic residue; and isolating the resulting compound of formula (IV).

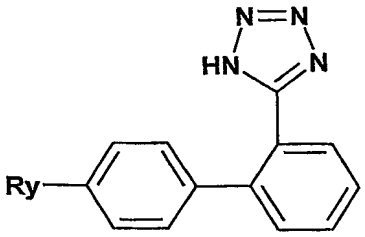
3. A process according to claim 1 for the manufacture of a compound of formula (IV b) comprising reacting a compound of formula (IV c)



(IV c)

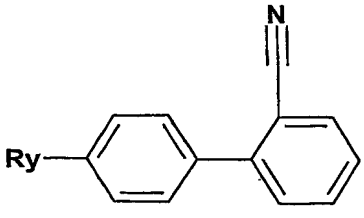
or an ester thereof with an azide of formula $(R_1)(R_2)M\text{-}N_3$ (IIb), wherein R_1 and R_2, independently of each other, have the meanings as defined above, and isolating the compound of formula (IV b).

4. A process according to claim 1 for the manufacture of a compound of formula



(VI)

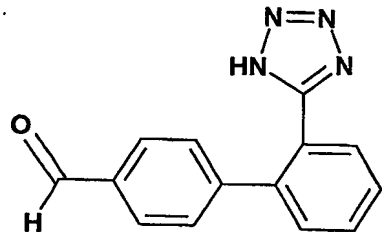
a tautomeric form thereof wherein Ry represents C_1-C_8-alkyl such as methyl; C_1-C_8-alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, formyl or an acetal thereof; comprising reacting a compound of formula (IV a)



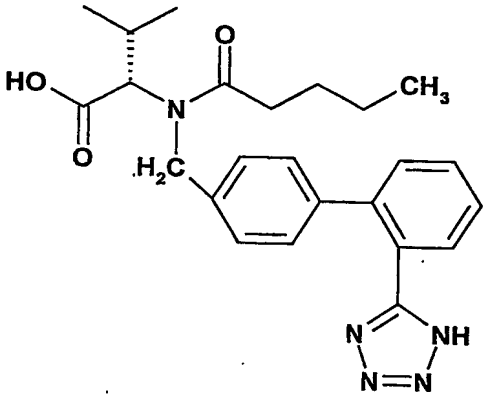
(VI a)

with a compound of formula **$(R_1)(R_2)M\text{-}N_3$ (II b)**, wherein R_1 and R_2, independently of one another, represent an organic residue; and isolating the resulting compound of formula (V).

5. A process for the manufacture of the compound of formula (VI)

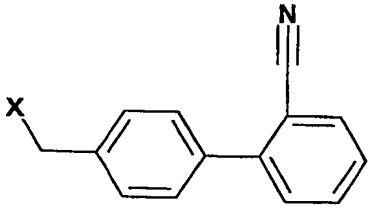


(VI)



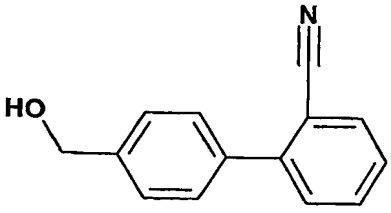
or a tautomer or salt thereof, comprising

(a) treating a compound of formula (VI a)



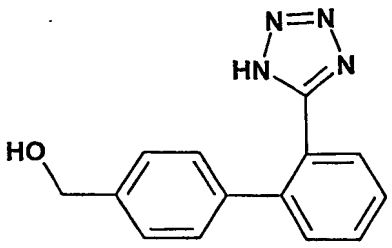
(VI a),

wherein X represents a leaving group, first with a nucleophilic agent and then with a "solvolytic" base resulting in a compound of formula (VI b)



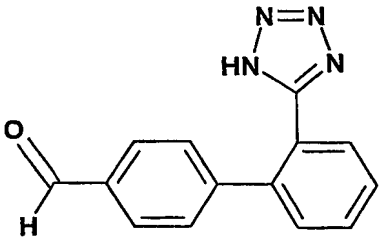
(VI b);

(b) reacting a compound of formula (VI b) with an azide of formula $(R_1)(R_2)M\text{-}N_3$ (II b), wherein the variables R_1 and R_2, independently of one another, have the meanings as defined above; resulting in a compound of formula (VI c)



(VI c) or a tautomer or salt thereof

(c) oxidizing a compound of formula (VI c) or a tautomer or salt thereof resulting in a compound of formula (VI)

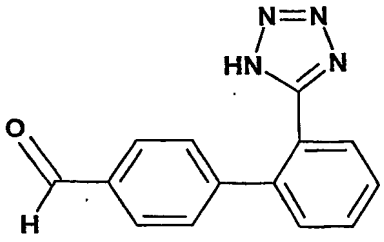


(VI)

or a tautomer or salt thereof; and

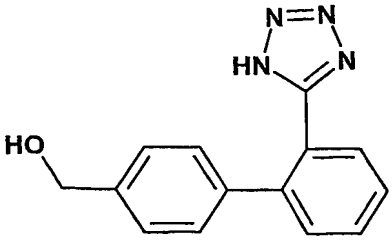
isolating the compound of formula (IV b) or a tautomer or salt thereof.

6. A process for the manufacture of a compound of formula (V d)



(VI)

comprising oxidizing a compound of formula (VI c)

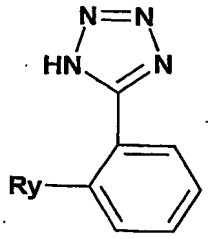


(VI c)

or a tautomer or salt thereof resulting in a compound of formula (VI) or a tautomer or salt thereof; and isolating a resulting compound of formula (VI).

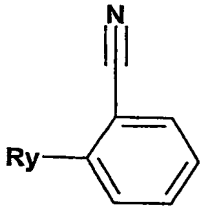
7. A process according to claim 5 or 6, wherein the oxidation is carried out in the presence of an oxidation agent selected from the group consisting of HNO_2, HNO_3 or a corresponding anhydride thereof, and a peroxodisulfate, and wherein as solvent an alkylated aromatic hydrocarbon solvent such as toluene is used.

8. A process according to claim 1 for the manufacture of a compound of formula



(VII)

a tautomeric form thereof, wherein Ry represents C_1-C_8-alkyl such as methyl; C_1-C_8-alkyl substituted by X' and X' being halogen, sulphonyloxy, hydroxyl, protected hydroxyl, such as bromomethyl, formyl or an acetal thereof; comprising reacting a compound of formula (VII a)



(VII a)

with a compound of formula **$(R_1)(R_2)M$-N_3 (II b)**, wherein R_1 and R_2, independently of one another, represent an organic residue; and isolating the resulting compound of formula (VI).

9. A process according to any one of claims 1 to 5 and 8, wherein a compound of formula **$(R_1)(R_2)M$-N_3 (II b)** is used, wherein M is aluminium or boron; and R_1 and R_2, independently of one another, is C_1-C_8-alkyl such as methyl, ethyl, propyl, diisobutyl, tert-butyl or n-octyl; C_3-C_7alkenyl such as allyl or crotyl, C_3-C_7-cycloalkyl such as cyclohexyl; phenyl-C_1-C_4-alkyl such as benzyl or 2-phenethyl; phenyl-C_3-C_5alkenyl such as cinnamyl, or C_3-C_8-cycloalkyl-C_1-C_8-alkyl such as cyclopropylmethyl or cyclohexylmethyl.

10. A compound of formula **$(R_1)(R_2)M$-N_3 (II b)**, wherein M is aluminium or boron; and R_1 and R_2, independently of one another, is C_3-C_7alkenyl such as allyl or crotyl, C_3-C_7-cycloalkyl such as cyclohexyl; phenyl-C_1-C_4-alkyl such as benzyl or 2-phenethyl; phenyl-C_3-C_5alkenyl such as cinnamyl, or C_3-C_8-cycloalkyl-C_1-C_8-alkyl such as cyclopropylmethyl or cyclohexylmethyl.

Abstract

The present invention relates to a method for preparing substituted tetrazoles, compounds obtained according to this method, new reactants and new tetrazole derivatives.